DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of the Secretary
Office of Public Health and Science

Office for Human Research Protections
The Tower Building
1101 Wootton Parkway, Suite 200
Rockville, Maryland 20852

Telephone: 301-402-5567
FAX: 301-402-2071
E-mail: mcarome@osophs.dhhs.gov

April 30, 2002

Robert Kay, M.D.
Chief of Staff
Vice Chairman, Board of Governors
The Cleveland Clinic Foundation
9500 Euclid Avenue
Cleveland, Ohio 44195

RE: Human Research Subject Protections Under Multiple Project Assurance (MPA) M-1388

Research Publications:
McCarthy, *et al.* Early Results with Partial Left Ventriculectomy. *J Thorac Cardiovasc Surg*. 1997; 114:755-765.

Franco-Cereceda, *et al.* Partial Left Ventriculectomy for Dilated Cardiomyopathy: Is This an Alternative to Transplantation. *J Thorac Cardiovasc Surg*. 2001; 121:879-893.

Dear Dr. Kay:

The Office for Human Research Protections (OHRP) has received The Cleveland Clinic Foundation's (the Clinic's) January 11 and February 27, 2002 reports that were submitted in response to OHRP's November 21, 2001 letter regarding the above-referenced research.

Based upon its review of these reports, as well as the Clinic's prior reports of August 30 and September 20, 2001, OHRP makes the following determinations regarding the activities described in the above-referenced publications:

(1) Department of Health and Human Services (HHS) regulations at 45 CFR 46.109(a) and

the Clinic's MPA require that all research involving human subjects that is not otherwise exempt under HHS regulations at 45 CFR 46.101(b) be reviewed and approved by the Clinic's Institutional Review Board (IRB).
HHS regulations at 45 CFR 46.102(d) define research as a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge. Activities which meet this definition constitute research for purposes of the Federal policy for protection of human subjects, whether or not they are conducted or supported under a program which is considered research for other purposes.

HHS regulations at 45 CFR 46.102(f) define a human subject as a living individual about whom an investigator conducting research obtains (i) data through intervention or interaction with the individual; or (ii) identifiable private information.

OHRP finds that the above-referenced publications described prospective, nonexempt human subject research that was conducted without being reviewed and approved by the Clinic's IRB. In specific, based upon statements in the above-referenced publications and the Clinic's reports, OHRP finds that investigators at the Clinic prospectively collected identifiable private information about living individuals in a systematic manner in order to develop generalizable knowledge about the safety and effectiveness of partial left ventriculectomy in the management of patients with dilated cardiomyopathy. Furthermore, OHRP acknowledges that the Clinic reached the same conclusion following its investigation of this matter.

Corrective Action: OHRP acknowledges that the Clinic has taken a number of corrective actions in response to the above finding, including the following: (a) the Clinic IRB has developed and adopted a new policy and application form for the processing of registries and data collection projects and has reviewed a large number of databases, including the database collecting cardiac surgery information; (b) a three-hour online research training course will be made mandatory for all clinical investigators at the Clinic; (c) the Clinic's Board of Governors has discussed the establishment of an Innovative Practice Committee that would review innovative, non-research treatments and triage research projects to the IRB; and (d) the Clinic has created a special Research Compliance Committee that will report to the Clinic's full Compliance Committee. OHRP finds that these corrective actions to be satisfactory and appropriate under the Clinic's MPA.

As a result of the above determinations, there should be no need for further involvement of OHRP in this matter. Of course, OHRP must be notified should new information be identified which might alter this determination.

At this time OHRP provides the following additional guidance:

(2) In accordance with HHS regulations at 45 CFR 46.116, whenever investigators obtain

identifiable private information on living individuals for a registry or database established solely, or in part, for research purposes, the informed consent of the subjects must be obtained from the subjects or the subjects' legally authorized representatives, unless this requirement has been waived by the IRB in accordance with HHS regulations at 45 CFR 46.116(c) or (d).

OHRP appreciates the continued commitment of your institution to the protection of human research subjects. Please do not hesitate to contact me should you have any questions.

Sincerely,

Michael A. Carome, M.D.
Director, Division of Compliance Oversight

cc: Dr. Floyd D. Loop, Chairman, Board of Governors, The Clinic
Dr. Alan Lichtin, Chair, IRB, The Clinic
Dr. Patrick McCarthy, The Clinic
Commissioner, FDA
Dr. David Lepay, FDA
Dr. Greg Koski, OHRP
Dr. Melody H. Lin, OHRP
Mr. George Gasparis, OHRP
Dr. Jeffrey Cohen, OHRP
Mr. Harold Blatt, OHRP
Mr. Barry Bowman, OHRP